REMARKS

1. The applicants have further added the limitation of "recovering with trypsin-EDTA" in Claim 1 to distinguish the invention from the method using Leukosorb filter, which recovers cells via elution from the filter using a buffer containing sodium citrate.

2. Regarding the obviousness rejection, the Office communication cited the prior arts of Caplan, Prockop and Matsui. However, there was no motivation or reason to combine these prior arts. Especially, Caplan (US 5811094) disclosed "the human bone marrow sample is then concentrated to remove plasma and cleared of red blood cells either by NH_4Cl treatment as described above or by passage of the samples over a Leukosorb™ filter contained in a syringe cartridge filter removing fat, red blood cells and plasma. The cell fraction retained by the filter is eluted from the filter using a buffer containing sodium citrate. The MSC enriched cells which elute from the filter are then further enriched by passage over a hydroxyapatite column which preferentially binds MSCs. The syringe filter eluate containing red blood cell depleted bone marrow is passed over a syringe filled with hydroxyapatite. The hydroxyapatite used in this example is obtained from Interpore Corp. (IP200). Porous hydroxyapatite granules having a minimum pore size of 200 micrometers and a maximum pore size of up to 500 micrometers are used." In other words, the teaching of Caplan was not only the use of Leukosorb to remove the red blood cells, but also included the further use of Porous hydroxyapatite, "having a minimum pore size of 200 micrometers and a maximum pore size of up to 500 micrometers." Indeed, there was no reason nor reasonable expectation of success to replace Caplan's Leukosorb filter with "10 micrometer isopore polycarbonate membrane" disclosed by Prockop.

3. Moreover, Prockop et al showed RS cells can be separated from other MSCs by ultrafiltration through an ultrafiltration membrane having appropriately-sized pores (e.g. 10 μm). However the example was done using a frozen stock of MSCs, which did not contain haematopoietic stem cells. In other words, these three prior arts were quite different from each other. There was no reasonable expectation of success in creating this application by referring to the teachings of Caplan and Prockop. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at , 82 USPQ2d at 1396. Therefore, the applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 USC §103.

4. Prockop's disclosure (US 7374937), which was very close to the application date of this application, did mention that "this review of the literature demonstrates that transplantation of MSCs have significant therapeutic and gene transfer uses. However, prior art methods for isolating MSCs and inducing their proliferation have practical limitations, including the extent of population expansion that can be achieved using prior art methods. There remains a critical need for methods of reliably inducing significant proliferation of MSCs in culture without inducing differentiation of the MSCs as they proliferate." In other words, this application did solve a problem that was long stannding in the art. (MPEP §716)

5. Caplan's disclosure (filed on 04/11/1995 and issued on 09/22/1998) did teach the ways of culturing MSC. How should a person skilled in the art would combine Matsui's culture device (filed on 10/11/1988 and issued on 10/03/1989) into Calpan's teachning? There was no reason nor reasonable expectation of success to modify the method of isolating MSC taught by Caplan with the culture dish taught by Matsui. Furthermore, Prockop's disclosure (US 7374937) also mentioned that "Despite the great interest in examining the biology of MSCs and their potential use for therapy, there is still no generally accepted protocol for isolating and expanding MSCs in culture. Most experiments relating to differentiation of MSCs have been performed using cultures of MSCs that have been isolated primarily by virtue of the MSCs tight adherence to tissue culture dishes, as described (Friedenstein et al., 1976, Exp. Hematol. 4:267-274; Friedenstein et al., 1987, Cell Tissue Kinet. 20:263-272). Others have attempted to prepare more homogenous MSC populations (e.g. Long et al., 1995, J. Clin. Invest. 95:881-887; Simmons et al., 1991, Blood 78, 55-62; Waller et al., 1995, Blood 85:2422-2435; Rickard et al., 1996, J. Bone Miner. Res. 11:312-324; Joyner et al., 1997, Bone 21:1-6). However, none of these protocols has gained wide acceptance. In addition, these protocols have been primarily designed to isolate osteoblast precursors. Use of these protocols has not been investigated to determine if they yield cells that are truly multipotential." In other words, these evidences did not supprt that one would have been motivated to make such a modification.

6. Your MPEP 201.13 stated "For U.S. applications filed prior to September 21, 2004, the incorporation by reference statement may appear in the transmittal letter or in the specification. The inclusion of this statement of incorporation by reference of the foreign priority application will permit an applicant to amend the U.S. application to include subject matter from the foreign priority application(s), without raising the issue of new matter." Therefore, the newly added claim 42 to limit the pore size to be 0.4 to 16 microns in diameter will not induce new matter.

Accordingly, this application should be placed in condition of allowance. An early Notice to this effect is respectfully expected.

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